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Origin and characterization of alpha smooth muscle actin-positive cells during murine lung development

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Abstract

© 2017 The Authors Stem Cells published by Wiley Periodicals, Inc. on behalf of AlphaMed Press ACTA2 expression identifies pulmonary airway and vascular smooth muscle cells (SMCs) as well as alveolar myofibroblasts (MYF). Mesenchymal progenitors expressing fibroblast growth factor 10 (Fgf10), Wilms tumor 1 (Wt1), or glioma-associated oncogene 1 (Gli1) contribute to SMC formation from early stages of lung development. However, their respective contribution and specificity to the SMC and/or alveolar MYF lineages remain controversial. In addition, the contribution of mesenchymal cells undergoing active WNT signaling remains unknown. Using Fgf10 CreERT2 , Wt1 CreERT2 , Gli1 CreERT2 , and Axin2 CreERT2 inducible driver lines in combination with a tdTomato flox reporter line, the respective differentiation of each pool of labeled progenitor cells along the SMC and alveolar MYF lineages was quantified. The results revealed that while FGF10 + and WT1 + cells show a minor contribution to the SMC lineage, GLI1 + and AXIN2 + cells significantly contribute to both the SMC and alveolar MYF lineages, but with limited specificity. Lineage tracing using the Acta2-CreERT2 transgenic line showed that ACTA2 + cells labeled at embryonic day (E)11.5 do not expand significantly to give rise to new SMCs at E18.5. However, ACTA2 + cells labeled at E15.5 give rise to the majority (85%–97%) of the SMCs in the lung at E18.5 as well as alveolar MYF progenitors in the lung parenchyma. Fluorescence-activated cell sorting-based isolation of different subpopulations of ACTA2 + lineage-traced cells followed by gene arrays, identified transcriptomic signatures for alveolar MYF progenitors versus airway and vascular SMCs at E18.5. Our results establish a new transcriptional landscape for further experiments addressing the function of signaling pathways in the formation of different subpopulations of ACTA2 + cells. Stem Cells 2017;35:1566–1578.

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Keywords

Alveolar myofibroblast, Lineage tracing, Lung, Lung development, Smooth muscle cell

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